

Message

From: Jerry Campbell [JCampbell@ramboll.com]
Sent: 12/4/2019 4:33:16 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; Harvey Clewell [HClewell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Walsh, Patrick [patrick-walsh@denka-pe.com]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Morozov, Viktor [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=03cc9abb639c453fab2bbb3e4617228-Morozov, Viktor]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; White, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e179825823c44ebbb07a9704e1e5d16-White, Paul]; Hawkins, Belinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=075561d171e845828ec67a945663a8e6-Hawkins, Belinda]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]
Subject: RE: Chloroprene PBPK: in vitro data / parameters

Paul,

As I look at the MCMC script for FRatKidney (I'm mostly not reviewing these, but just to understand what was done), it looks like a distribution for the loss rate is being sampled during the parameter estimation. Is this distribution being treated as fixed, or updated based on the particular data set? It might be narrow enough not to matter.

The posterior distribution was fixed (see previous email) and based on a posterior chain that encompassed 8 experiments. Since all experiments were run at the same time, the background across all vials (not individual experiments within the total experiment) would be the most accurate distribution of loss. You cannot treat a single vial/vial experiment as a matched control. That's not how variability in an experiment like this works. The posterior chain of background loss that was sampled encompassed the totality of uncertainty in the overall experiment background loss. Coupling this with the experimental data with metabolism is the best approach to incorporate RLOSS into the MCMC. This is also why the simple Nelder-Meade approach is not acceptable as that only allowed for a fixed (mean of the posterior) to be used and, thus, does not include uncertainty in the background loss.

Also, in the results spreadsheets, the Female Rat Kidney plot leaves out the lowest concentration data and simulation results, initial value = 0.09 uM. It looks OK, but I was looking at the MCMC file to check if those data had been used in the parameter estimation, which looks like the case. The results I get are below, underpredicts metabolism a bit at that lowest concentration, but the fit is to the whole data set very well. The figure should just be updated.

We will update the figure.

A linear-y plot of the same results is 2nd below. (The little 'jags' are due to the sampling pulling out CP at each time-point.) For the highest concentration data/simulation, the amount attributed to system loss, ARLOSS, is 5.9 times the amount attributed to metabolism, so it's the predominant pathway. That the concentration decline predicted is slightly faster than the data suggest that the actual loss rate was lower in the experiment.

A loss rate that better fits the high-concentration kidney data is 0.001 instead of 0.0014, but then the metabolic clearance at lower concentrations is more underpredicted (3rd plot below). The kidney is least important, so this probably doesn't matter much... For the female mouse lung the clearance at the highest concentration is over-predicted a bit too, but over the entire data set those results are much less sensitive to the term.

So I don't think it's worth much additional work. But it just seems odd that with all the other attention to detail, a few more control experiments weren't run. And overly precise to have a rate constant to 4 significant figures when there's probably more uncertainty than that.

I don't think your observation here is correct. There were no metabolism vials run with all experiments. The RLOSS posterior distribution is derived from a posterior distribution that was assessed from 8 experiment which totaled 34 vials without metabolism. This was the best approach to incorporate background loss into the MCMC as there is no way to know exactly what the background loss in a specific vial with metabolism was. One can only assume that it fell within the overall background loss uncertainty of the experiments. The point behind the analysis is to incorporate all of the uncertainty into the best estimate of metabolism. Parsing data that were collected at the same time under the same conditions would not be making use of the information to define RLOSS.

Jerry Campbell

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>

Sent: Tuesday, December 3, 2019 3:27 PM

To: Harvey Clewell <HClewell@ramboll.com>

Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; Cynthia Van Landingham <cvanlandingham@ramboll.com>

Subject: RE: Chloroprene PBPK: in vitro data / parameters

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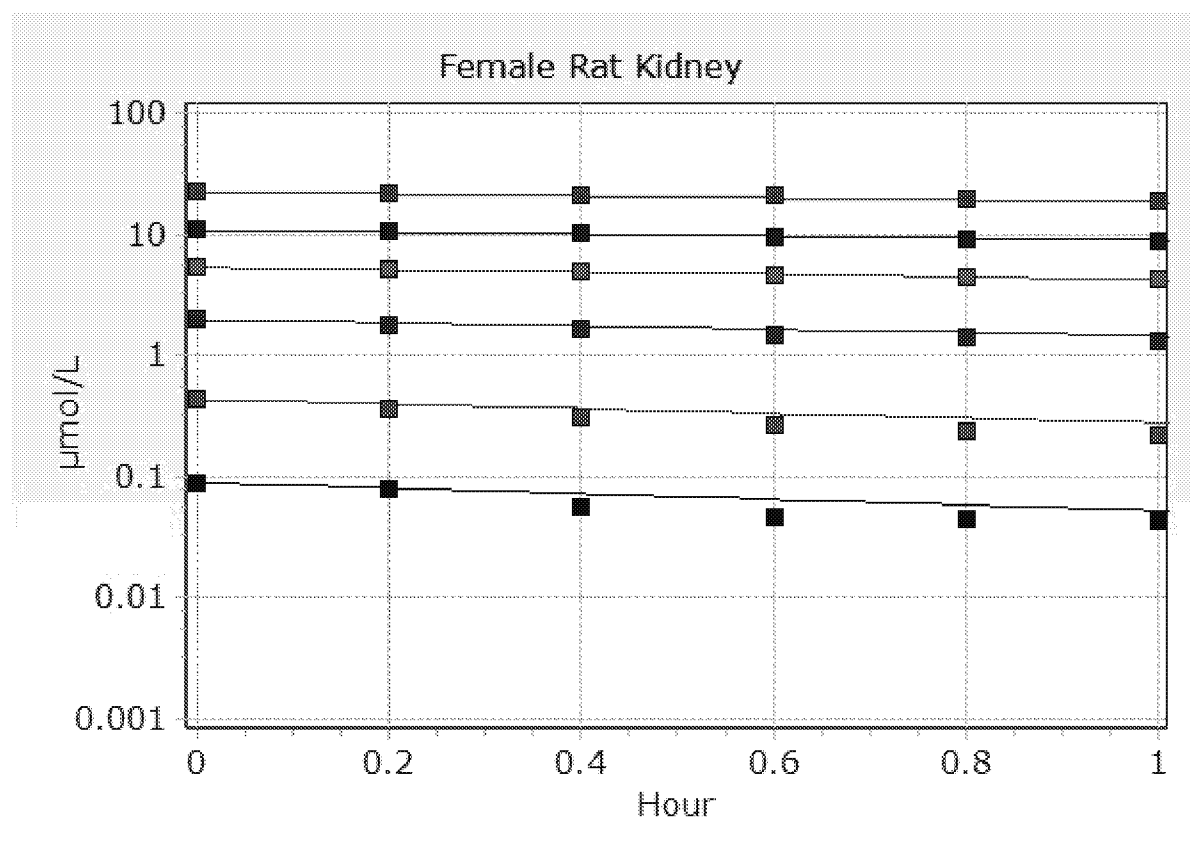
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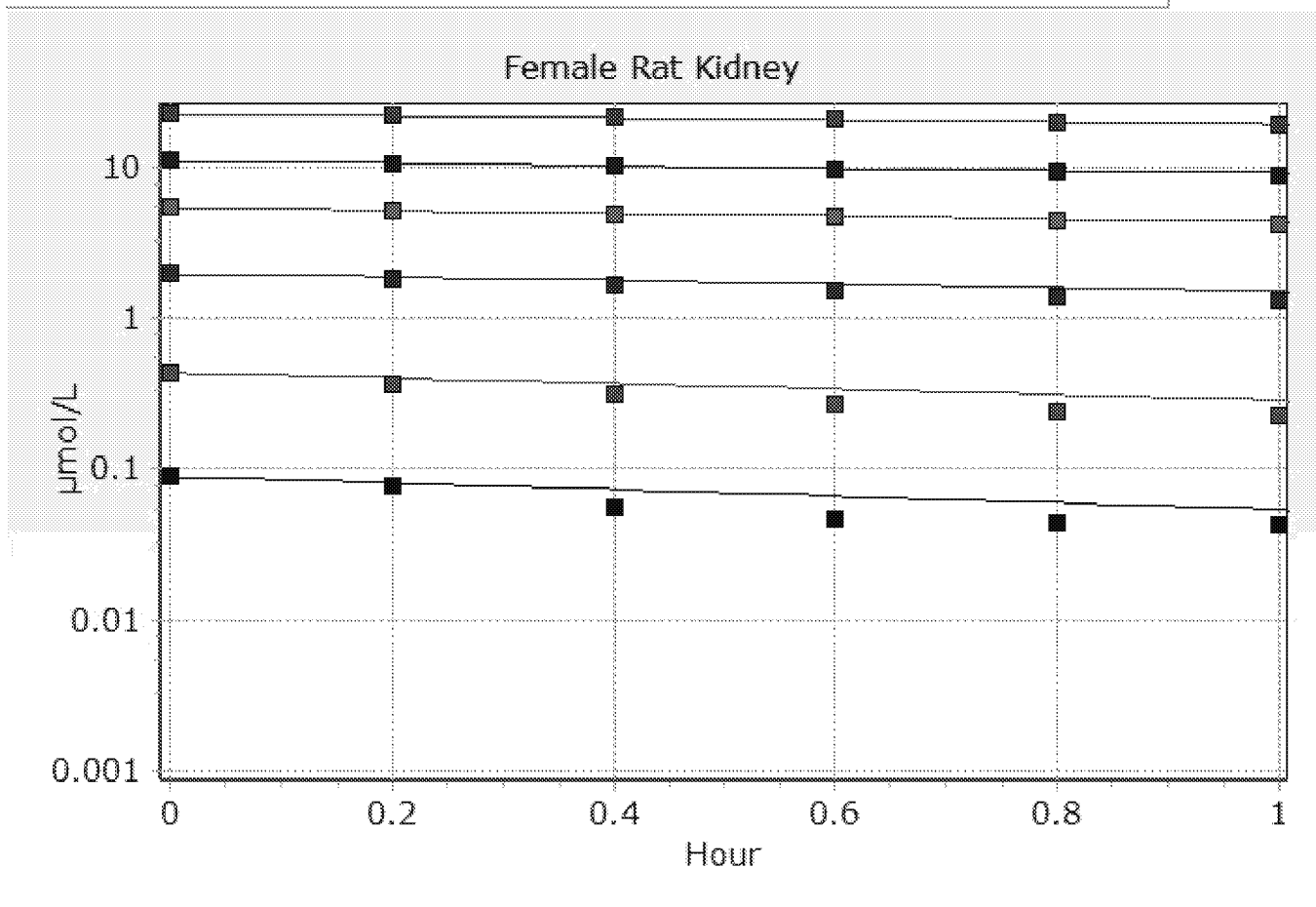
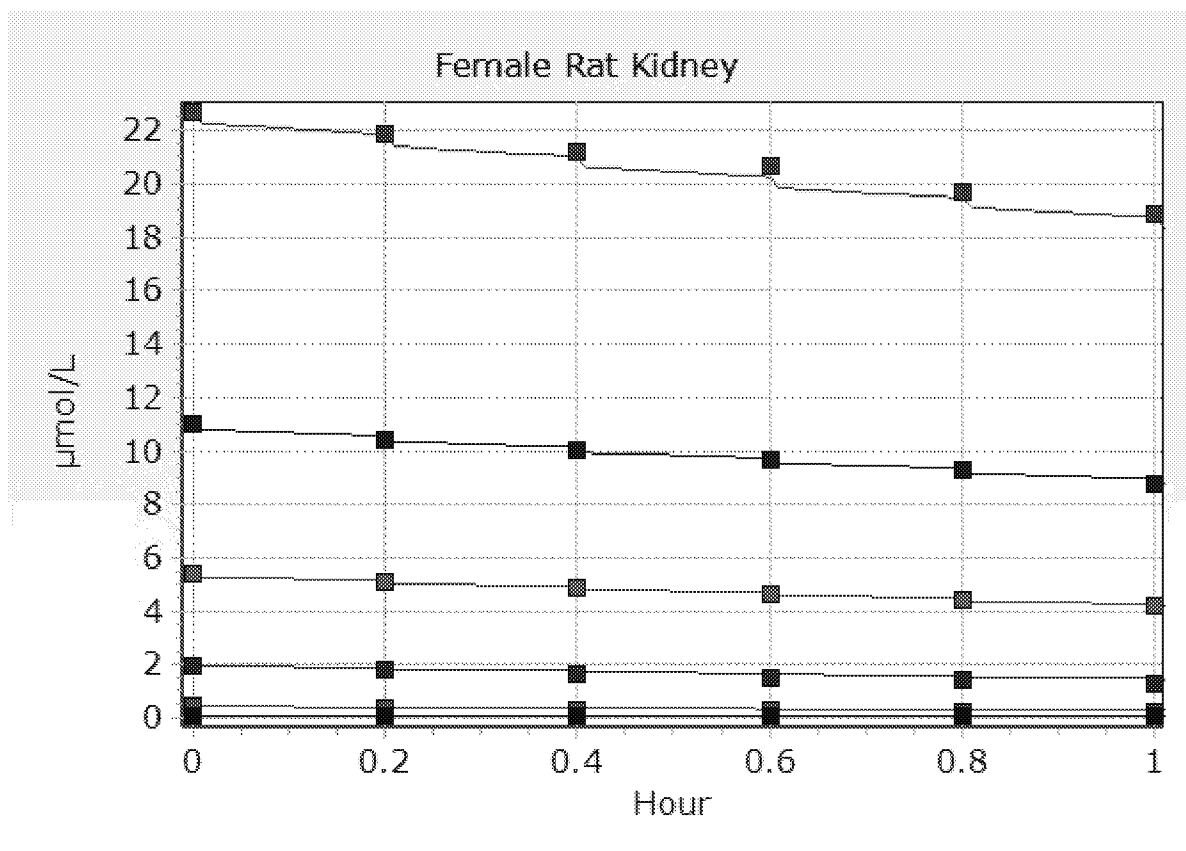
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-Paul





From: Harvey Clewell <HClewell@ramboll.com>
Sent: Tuesday, December 03, 2019 1:57 PM

To: Schlosser, Paul <Schlosser.Paul@epa.gov>

Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; cvanlandingham@ramboll.com

Subject: RE: Chloroprene PBPK: in vitro data / parameters

Jerry, you're up!

Sorry.

With kind regards

Harvey Clewell

PhD, DABT, FATS

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>

Sent: Tuesday, December 3, 2019 1:41 PM

To: Harvey Clewell <HClewell@ramboll.com>

Cc: Jerry Campbell <JCampbell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>; Cynthia Van Landingham <cvanlandingham@ramboll.com>

Subject: RE: Chloroprene PBPK: in vitro data / parameters

Harvey, all,

This is fairly small but niggling thing: when the 2nd set of experiments were run, the incubation vials were slightly different (smaller volume) and the sampling volume, maybe the syringes, used were different. In the model files difference in vial volume, < 0.3 mL, is tracked. But the system loss rate, which might depend on small things (e.g., quality of seal formed by the vial cap) is assumed to be unchanged. Do you recall if any control incubations were done in 2009, that could be used to check that? I don't see any data in the Yang paper or Matt's report.

For the female mouse lung the loss is about 15% of the metabolic conversion, so it's not a huge factor. But as I go through the QA and see the VVIAL set to slightly different values for the two sets of experiments (and this makes a small but noticeable difference in the plots), it stands out that RLOSS, which is set to 4 significant figures, is assumed to be exactly the same.

-Paul

From: Cynthia Van Landingham <cvanlandingham@ramboll.com>

Sent: Monday, November 18, 2019 2:00 PM

To: Schlosser, Paul <Schlosser.Paul@epa.gov>

Cc: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>;

Hawkins, Belinda <Hawkins.Belinda@epa.gov>

Subject: RE: Chloroprene PBPK: metabolic parameters / IVIVE calculations

Paul,
Attached is the paper that you requested in your e-mail below. I will get back to you as soon as I can with the answers to your other questions.

Cynthia

Cynthia Van Landingham

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>

Sent: Monday, November 18, 2019 1:38 PM

To: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>

Cc: Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>

Subject: Chloroprene PBPK: metabolic parameters / IVIVE calculations

Greetings,

While I can't speak to the ultimate numerical significance, there are a number of discrepancies in and among the descriptions and calculations for IVIVE of metabolic parameters (i.e., between statements in the main report, p. 9, Supp Mat C, and the spreadsheet, Supp Mat D), and a couple of choices that I'm questioning. See below.

I would need to request a copy of Houston and Galetin (2008), which might take a few days, so it would help if Ramboll can send a copy.

I've highlighted the items that seem most significant, where corrections in the IVIVE spreadsheet appear to be needed or the justification (40 vs. 45 mg/g microsomal protein in rat liver) seems a bit weak. A copy of the spreadsheet where I've highlighted cells of concern is attached.

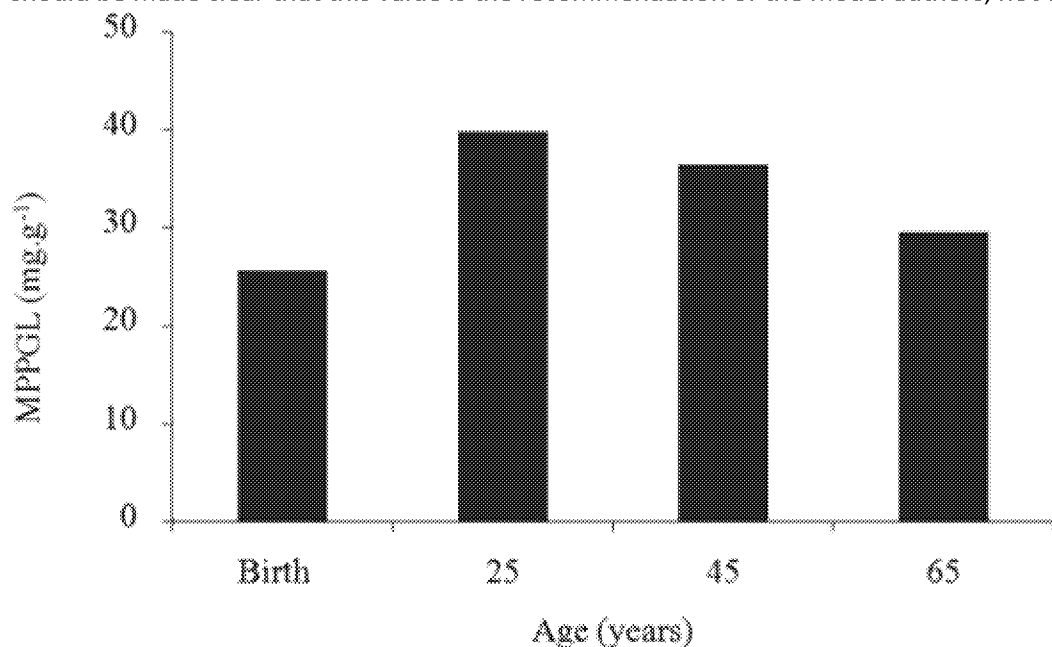
-Paul

Metabolic parameters and IVIVE extrapolation

The following are found in the spreadsheet, EPA Supp Mat D, in the "IVIVE" tab.

- **BW values for mice and rats, cells C22-C25:** these differ from the standard BW values listed in table S-1. For the sake of consistency, and since the tissues used to obtain microsomes were likely from juvenile/young adult animals, it might be better to use the lower, standard BW values from Table S-1. Alternately the Supp Mat C, Table 1 (which match the values in the Supp Mat D, IVIVE table), should be used in the model code for dose calculations in the absence of study-specific values.
- **Liver and lung microsome content, cells G22-G27 (liver) and cells H22-H26 (lung in all species):**
 - **Mouse liver:** From Supp Mat C, value of 35 mg/g is from Medinsky et al. (1994), so reference in cell G27 is incorrect (says "rat value used for mouse")
 - **Rat liver:**
 - report p. 9 says 45 mg/g used for rats, not consistent with 40 in IVIVE spreadsheet (cells G24-25);
 - need to obtain Houston and Galetin (2008);

- Supp Mat C says an average of values for rat from Medinsky et al. (1994) (sentence is confusing, “For mouse, 35 mg/g liver was reported by Medinsky et al. (1994) for both rat and mouse,”) and 45 mg/g from Houston and Galetin, but it’s not entirely clear why a cross-species average would be used for the rat, but not the mouse ; if Medinsky et al. (1994) also measured 35 mg/g from rat liver, then an average may make sense...
- In Barter et al. (2007), Figure 2, part A, there appear to be many papers reporting 45 mg/g for the rat, so the value of 45 mg/g may be better supported;
- reference in cell 27 just cites Houston and Galetin (2008), not consistent with “40”.
- **Human liver:**
 - Text in main report, p. 9, says 40 mg/g, which matches the value listed in Supp Mat C;
 - But IVIVE cell G26 has **50 mg/g**;
 - Supp Mat C, “Based on their meta-analysis and consensus report of the human data (Barter et al., 2007), 40 mg/g liver is recommended for human adults for chloroprene IVIVE-PBPK modeling,” so it would be less confusing if the main report and IVIVE cell G27 cited this reference, not Barter et al. (2008)
 - From Barter et al. (2007): “Values of MPPGL were approximately 36 and 31% lower in newborn and elderly (80 years) individuals than those in a 25-year-old individual (typically the age of individuals used in clinical pharmacology studies). The use of a value of MPPGL of 40 mg g⁻¹, determined for a young adult, would be expected to result in an overprediction of clearance in very young or very old patients. Therefore, MPPGL values relevant to the age of the population in which predictions are being made should be used in IVIVE.” Image below is from Barter et al. (2008). Should risk assessment be focused on young adults, or entire population; i.e., use more of a population-average value from this reference? The young-adult value of 40 mg/g likely will be most health-protective.
 - But the statement in Supp Mat C appears to mis-represent the conclusions of Barter et al. (2007): it should be made clear that this value is the recommendation of the model authors, not the cited paper.



- **Lung:** value of 23 mg/g in cells H22-26 does match Himmelstein et al. (2004b), but text in the report says 20 mg/g, and this is the conclusion after some discussion in Supp Mat C. Hence it appears that the value in the IVIVE tab (used) should be 20 mg/g and the reference in cell H27 should be changed to Medinsky et al. (1994).
- **In Vitro Values of KFLUC for female rat (cell V33) and male rat (cell V38):** These cells have calculations which are not explained and do not take values from the in vitro metabolic results; e.g., “=1.2/(0.82*2)/1000” in cell V33, which should be just equal to Parameter_Summary cell I18.

